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Enaminone-directed ruthenium(II)-catalyzed C–H activation and annulation of arenes with diazonaphthoquinones for polycyclic benzocoumarins†

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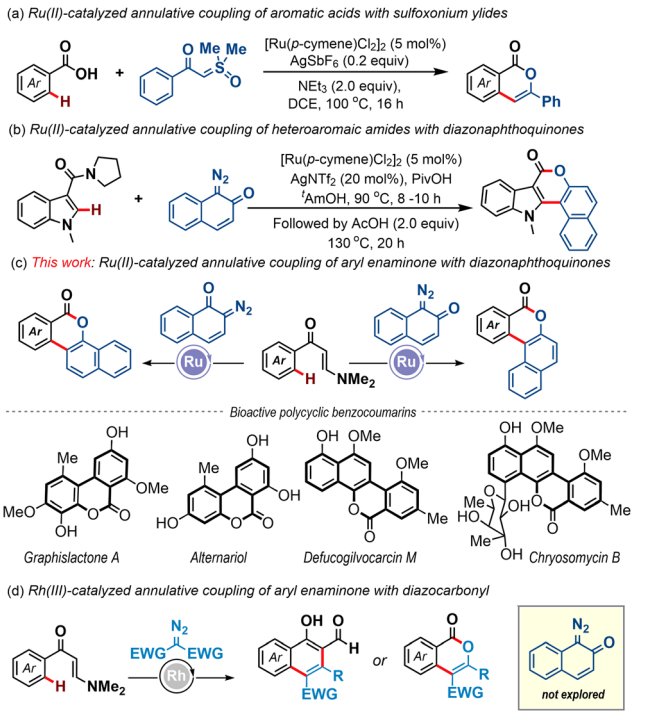
The weakly coordinating enaminone functionality has been leveraged for a C–H bond activation strategy under ruthenium catalysis and employed in the regioselective annulative coupling of arenes with diazonaphthoquinones, offering polycyclic benzocoumarins in very high yields. The enaminone motif plays a dual role and the protocol operates through a Ru(II)/Ru(IV) catalytic pathway which is amenable to the diversification of various pharmacophore-coupled substrates.

Over the past two decades, transition-metal-catalyzed site-selective inert C–H bond activation and annulation strategies have revolutionized the field of synthetic chemistry, offering powerful tools for the construction of high-value carbocycles and heterocycles from simple molecular building blocks.[1] In this context, Ru(II)-catalysis has emerged as a particularly compelling choice, garnering widespread attention for its operational simplicity, cost-effectiveness, and impressive efficiency facilitated by weak coordination.[2] However, the major advancements in the C–H bond activation guided annulation reactions of Ru(II)-catalysts have been accomplished with alkynes and alkenes with key applications in the synthesis of bioactive compounds.[2,3] In contrast, the progress of such annulation reactions engaging carbene species that require the involvement of high-valent ruthenium(IV) intermediates is very limited.[4] This is especially true when a weakly coordinating directing group is considered. An early example was disclosed by the Ackermann group wherein aromatic acids were coupled with sulfoxonium ylides, leading to the formation of functionalized isocoumarins in high yields (Scheme 1a).[5] More recently, Samanta *et al.* demonstrated an amide-directed annulative coupling of azaheterocycles, such as indoles, with diazonaphthoquinones to afford diverse azacoumestans (Scheme 1b).[6] However, in the latter case, the lactonization event was performed in a subsequent step in the presence of AcOH at 130 °C. To the best of our knowledge, these two examples represent the sole instances of Ru(II)-catalyzed annulation reactions of carbenes operating under the guidance of weakly coordinating directing groups.

Polycyclic benzocoumarins and derivatives thereof hold immense synthetic importance in light of their existence in natural products and pharmaceuticals.[7,8] Consequently, the development of efficient synthetic protocols *en route* to these scaffolds is highly desirable.[8] Herein, we report an annulative coupling of readily prepared aryl enaminones with diazonaphthoquinones as a concise route towards high-value polycyclic benzocoumarin motifs (Scheme 1c). Notably, the present work represents the first



Scheme 1 The C–H activation and annulative coupling reactions with carbene species assisted by weak coordination.

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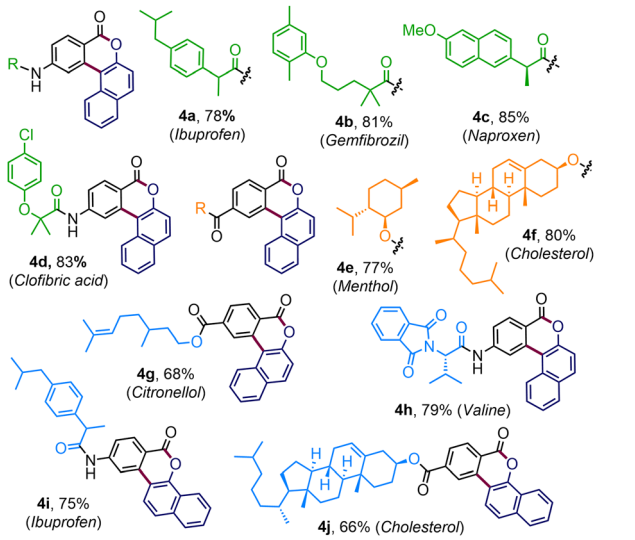
application of the enaminone functionality as a directing group in ruthenium-catalyzed C–H activation strategies and the enaminone group serves as an intriguing one-carbon synthon to effect the desired annulation event in one pot. Of note, Zhu *et al.* first introduced the enaminone motif as a directing group under Rh-catalysis to access functionalized naphthalenes and the major developments towards C–H activation reactions involving the enaminone directing group have been confined to require expensive Rh-catalysis (Scheme 1d).[9] Also, our work showcased the reactivity of enaminone-bearing metallacycles in combination with quinoid carbene species, which has not been previously studied.[9,10]

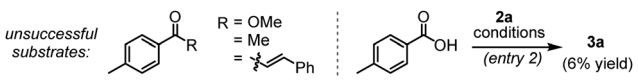
We commenced our investigation following the model reaction between (*E*)-3-(dimethylamino)-1-(*p*-tolyl)prop-2-en-1-one (**1a**) with diazonaphthoquinone **2a** (Table 1). When the mixture of **1a** and **2a** was treated with a catalytic amount of $[Ru(p\text{-cymene})Cl_2]_2$ in the presence of $AgSbF_6$ (20 mol%), K_2CO_3 (0.5 equiv.) and 1-adamentanecarboxylic acid (1-$AdCO_2H$, 0.2 equiv.) in MeOH at 100 °C, we did not detect any product formation with the recovery of **1a** (entry 1). However, a substantial amount of tetracyclic benzocoumarin **3a** was formed in CF_3CH_2OH solvent (entry 1) and the reaction yield improved significantly in hexafluoroisopropanol (HFIP) medium, furnishing the desired product **3a** in 94% isolated yield (entry 2). On the contrary, the reaction was unsuccessful in aprotic solvents such as toluene, DCE, and THF (entry 3). Further screening of other bases gave inferior results (entry 4). The change of acid additive from 1-$AdCO_2H$ to AcOH or 2,4,6-trimethylbenzoic acid ($MesCO_2H$) also reduced the productivity (entry 5). The reaction at a lower temperature (80 °C) delivered **3a** only in 68% yield (entry 6). The amount of K_2CO_3 turned out to be critical as the reaction with a higher loading of K_2CO_3 (1 equiv.) resulted in poor conversion (entry 7). Nonetheless, control experiments suggested that both K_2CO_3 and 1-$AdCO_2H$ were crucial to achieving the high yield (entries 8 and 9) and the reaction completely shut down in the absence of $AgSbF_6$ and ruthenium(II) catalyst (entries 10 and 11). Interestingly, the reaction was unproductive with Cp*Co(III)-catalyst, while we have found moderate reactivity with the Rh(III)-catalyst leading to **3a** in 59% yield (entry 12). Furthermore, the enaminone motif is highly important for this C–H bond activation/annulation reaction, and our attempts to induce the coupling of **2a** with other carbonyl compounds, which include aromatic ester, ketone, and chalcone derivatives, were so far unsuccessful, while the reaction with the aromatic acid gave the desired product **3a** only in 6% yield (Table 1).[6,9i]

Having acquired the optimized conditions (Table 1, entry 2), we next investigated the substrate scope (Table 2). The protocol is quite general accommodating a wide range of arene-substituted enaminones. The reactions proceeded smoothly with substrates bearing electron-donating substituents such as alkyl (**3b–d**), methoxy (**3e**), tosyl (**3f**) and benzyloxy (**3g**) in the aryl ring to deliver the

Table 1 Optimization of the annulative coupling reactions[a]

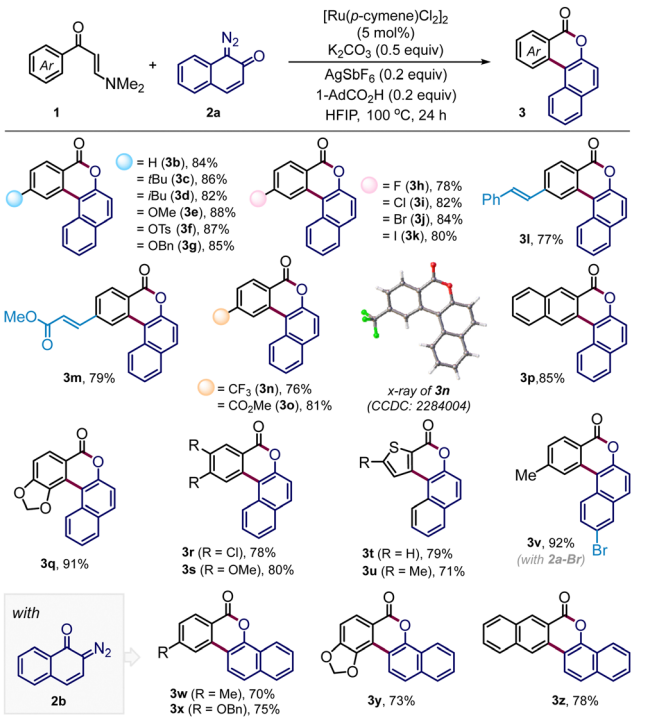


Entry	Deviation from standard conditions	Yield[b] (%)
1	$MeOH/CF_3CH_2OH$ instead of HFIP	NR/72
2	**None**	**94**
3	Toluene/DCE/THF instead of HFIP	NR
4	$Na_2CO_3/KOAc/K_3PO_4$ instead of K_2CO_3	40/65/NR
5	$AcOH/MesCO_2H$ instead of 1-$AdCO_2H$	47/56
6	At 80 °C	68
7	K_2CO_3 (1 equiv.)	60
8	Without K_2CO_3	41
9	Without 1-$AdCO_2H$	43
10	Without $AgSbF_6$	NR
11	Without Ru(II)-catalyst	NR
12	$Cp^*Co(CO)I_2/[Cp^*RhCl_2]_2$	NR/59



[a] Reaction conditions: **1a** (0.20 mmol), **2a** (1.5 equiv.), solvent (1 mL) for 24 h. [b] Isolated yields. NR: no reaction with the recovery of **1a**.

Table 2 Exploration of substrate scope



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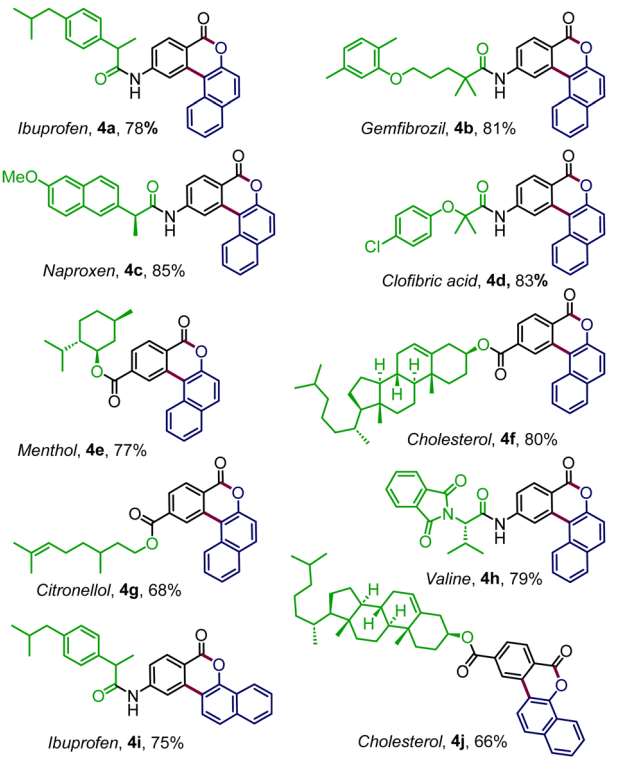
desired polycyclic benzocoumarins in very high yields (82–88%). The halogen functionalities such as fluoro (**3h**), chloro (**3i**), bromo (**3j**), and iodo (**3k**) were undisturbed under the reaction conditions and these halogen functionalities are useful synthetic handles for further functionalization. The presence of sensitive olefin functionalities also did not interfere with the annulation reaction, offering **3l** and **3m** in 77% and 79% yields, respectively. Satisfyingly, substrates with electron-withdrawing groups, which include trifluoromethyl and carboxylate ester, also effectively participated in this reaction, dispensing **3n** and **3o** in very high yields. The product **3n** was crystalized and the presence of a polycyclic benzocoumarin framework was unambiguously confirmed through single crystal X-ray analysis. 2-Naphthyl-derived enaminone produced pentacyclic compound **3p** in 85% yield where the reaction took place at the sterically less hindered site. On the other hand, annulation occurred at the more hindered site for the piperonyl-substituted enaminone to give **3q** in 91% yield. This change in the regioselectivity can be attributed to the anchimeric assistance through the bridge oxygen.[11] For other enaminones having dichloro or dimethoxy substituents, the reactions proceeded at the less hindered site, forging **3r–3s** with high efficiency. Heterocyclic substrates such as thiophene enaminones were also compatible to afford **3t** and **3u** in 79% and 71% yields, respectively. Variation in the diazonaphthoquinone coupling partner was also considered. The reaction with 6-bromo-1-diazonaphthalen-2(1*H*)-one (**2a-Br**) furnished the desired coumarin **3v** in excellent yield. Gratifyingly, under the standard reaction conditions, the annulation reaction was also fruitful with diazonaphthoquinone **2b**, a regioisomer of **2a**, and we have successfully prepared polycyclic benzocoumarins **3w–3z** in high yields (Table 2).

To expand the reaction scope further, enaminone embedded with various biologically relevant scaffolds was examined (Table 3). To our delight, enaminones coupled with commercial drugs, for instance, ibuprofen, gemfibrozil, clofibric acid, and naproxen, effortlessly afforded the desired products **4a–4d**, in good to high yields. The standard conditions were also well suited for the enaminones derived from biorelevant motifs like menthol (**4e**), cholesterol (**4f**), and citronellol (**4g**). The strategy was equally productive with enaminone connected to valine amino acid where the polycyclic benzocoumarin **4h** was obtained in 79% yield. Similarly, the pharmacophore-tethered annulated products **4i–4j** were prepared in good yields by coupling diazonaphthoquione **2b** (Table 3).

The synthetic utility was further showcased through post-synthetic manipulations (Scheme 2a). Satisfyingly, treatment of polycyclic benzocoumarins **3a–b** with Lawesson's reagent furnished thiocoumarin analogs **5a–b** in excellent yields. Product **3a** was also transformed into polycyclic benzochromene **6** in 95% yield through $NaBH_4$ reduction (Scheme 2a, right).

To understand the nature of the C–H metallation step, deuterium incorporation experiments were performed. The reaction of enaminone **1a** with **2a** under standard reaction conditions for 12 h in the presence of deuterated acetic acid (10.0 equiv.) resulted in a significant amount of deuterium incorporation, indicating that the C–H ruthenation process is reversible (Scheme 2b). The competitive experiment with electron-rich and

Table 3 Synthesis of pharmacophore tethered polycyclic benzocoumarins[a]



[a] Reaction conditions: **5** (0.2 mmol), **2a** or **2b** (1.5 equiv.), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), 1-AdCO_2H (0.2 equiv.), $AgSbF_6$ (0.2 equiv.), K_2CO_3 (0.5 equiv.) and HFIP (1 mL) at 100 °C for 24 h.

electron-deficient enaminones gave a 1.4 : 1 mixture of benzocoumarins **3e** and **3n**, signifying that the C–H metallation step most likely follows a concerted metallation deprotonation (CMD) pathway (Scheme 2c). Employing the Ru(II)-cationic complex {[Ru(*p*-cymene)$(MeCN)_3$]$(SbF_6)_2$} instead of a combination of [Ru(*p*-cymene)Cl_2]$_2$ dimer and $AgSbF_6$, we have isolated the annulated product **3a** in 76% yield, suggesting the indispensable role of the cationic Ru(II)-complex in this transformation (Scheme 2d). Based on these results and literature precedents, a plausible reaction mechanism has been proposed in Scheme 2e. First, a cationic ruthenium complex is formed through the ligand exchange event and it then initiates the C–H activation reaction with enaminone **1** to give five-membered ruthenacycle **A**. Next, intermediate **A** reacts with diazonaphthoquinone **2a** to generate the carbenoid intermediate **B** and the subsequent migratory insertion provides six-membered intermediate **C**. Finally, protodemetallation followed by aromatization delivers **D** which cyclizes under the reaction conditions to produce the desired product **3**.

In summary, we have exploited the versatile enaminone functionality as a directing group for C–H bond activation the reaction under ruthenium catalysis and successfully devised an annulation reaction with diazonaphthoquinones, offering biologically relevant polycyclic benzocoumarins in very high to excellent yields. The protocol is operationally simple, displays a broad substrate generality and functional group compatibility,

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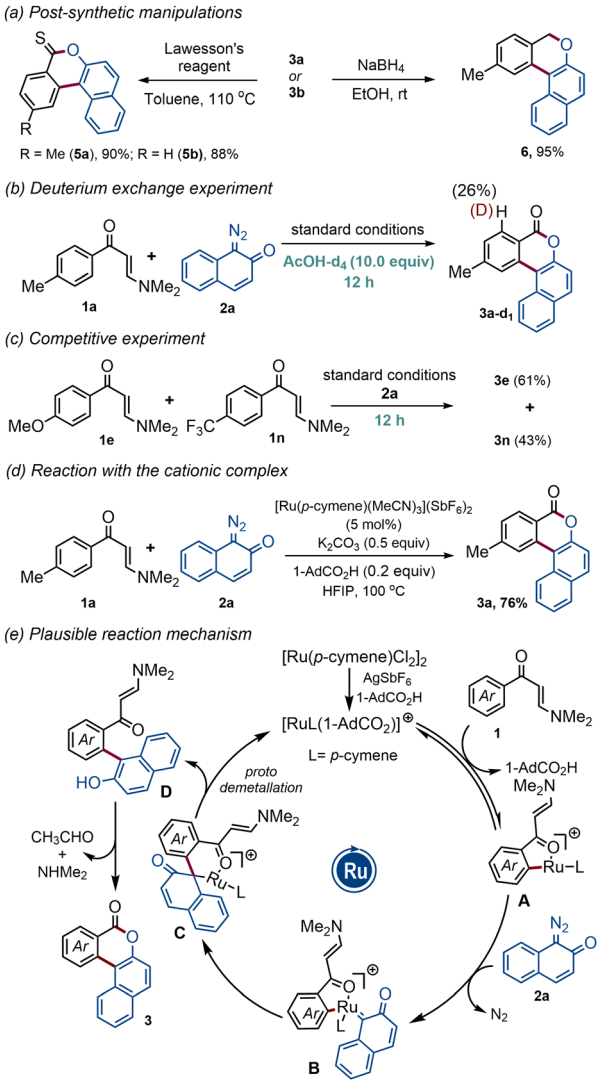

Scheme 2 Post-synthetic manipulations, mechanistic study, and reaction mechanism.

and is also effective in the diversification of substrates bearing bioactive scaffolds and natural product motifs. The protocol leverages the dual role of the enaminone functionality and involves a ruthenium(II)/(IV) catalytic pathway involving quinoid carbene species.

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Conflicts of interest

There are no conflicts to declare.

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